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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/579,607	05/16/2006	Susanne Moira Brown	6947-75758-01	9408

24197 7590 11/18/2008

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EXAMINER	
NGUYEN, QUANG	
ART UNIT	PAPER NUMBER
1633	
MAIL DATE	DELIVERY MODE
11/18/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/579,607	BROWN ET AL.	
	Examiner	Art Unit	
	QUANG NGUYEN, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *1* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 August 2008*.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1, 3, 6-9, 11-15, 17-35, 40, 46-48, 50-51, 54-57, 59-63, 65-84, 86-103, 105-119* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1,3,6-9,11-15,17-35,40,46-48,50,51,54-57,59-63,65-84,86-103 and 105-119.

DETAILED ACTION

Applicant's amendment filed on 8/19/2008 was entered.

Amended claims 1, 3, 6-9, 11-15, 17-35, 40, 46-48, 50-51, 54-57, 59-63, 65-84, 86-103, 105-108 and new claims 109-119 are pending in the present application.

In light of the excessive number of pending claims in the present application (**about 95 claims**) and amendments to the claims, the following new restrictions are required.

Election/Restrictions

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claims 1, 3, 6-9, 11-15, 17-31, 40, 47 and 109, drawn to a recombination nucleic acid vector having specific components recited in independent claim 1; a medicament and a kit comprising the same recombination vector of claim 1.

Group II, claims 32-35 and 110-112, drawn to a method of generating a herpes simplex virus which expresses a nucleotide sequence of interest using the vector of claim 109.

Group III, claims 48, 50-51, 54-57, 59-63, 65-84, 46, 87-88, 106-108 and 113, drawn to a herpes simplex virus (HSV) wherein the herpes simplex virus comprises a nucleic acid cassette integrated in the RL1 locus of the HSV genome and comprising the specific components recited in independent claim 48; a medicament comprising the same.

Group IV, claims 89-96 and 114, drawn to a method of generating a recombination nucleic acid vector having the specific steps recited in independent claim 89.

Group V, claims 97, 100, 115-119, 101-103 and 105, drawn to a method of generating a mutant HSV comprising inserting a nucleic acid cassette having the specific components recited in independent claim 97.

Group VI, claims 98-99, drawn to a method of generating a mutant herpes simplex virus comprising a nucleic acid cassette into a predetermined insertion site in the RL1 locus of the genome of a selected HSV using the recombination vector of claim 1.

Group VII, claim 86, drawn to a method of lysing or killing tumor cells in a patient in need of treatment using an effective amount of the herpes simplex virus of claim 48.

The technical feature linking Groups I-VII appears to be that they all relate to a recombination nucleic acid vector comprising first and second nucleotide sequences corresponding to nucleotide sequences flanking a predetermined insertion site in the RL1 locus (RL1 gene encoding for ICP34.5) and a cassette located between said first and second nucleotide sequences comprising the specific components recited in independent claim 1.

The inventions listed as Groups I-VII do not related to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

37 CFR 1.475(b) states:

"An international or a national stage application containing claims to different categories of invention will be considered to have unity of invention if the claims are drawn only to one of the following combinations of categories:

(1) A product and a process specifically adapted for the manufacture of said product; or

(2) A product and process of use of said product; or

(3) A product, a process specifically adapted for the manufacture of the said product, and a use of said product; or
(4) A process and an apparatus or means specifically adapted for the manufacture of the said product; or
(5) A product, a process specifically adapted for the manufacture of the said product, and an apparatus or means specifically designed for carrying out the said process."

Furthermore, according to the PCT Rule 13.2, unity of invention exists only when there is a shared same or corresponding special technical feature among the claimed inventions. The "Instructions Concerning Unity of Invention" (MPEP, Administrative Instructions Under the PCT, Annex B, Part 1 (b) state, "The expression of 'special technical features' is defined in Rule 13.2 as meaning those technical features that define a contribution which each of the inventions, considered as a whole, makes over the prior art.". Thus, unity of invention exists only when the shared same or corresponding technical features is a contribution over the art. Administrative Instructions Under the PCT, Annex B state, If…an independent claim does not avoid the prior art, then the question whether there is still an inventive link between all the claims dependent on that claim needs to be carefully considered. If there is no linkage remaining, an objection of lack of unity a *posteriori* (that is, arising only after assessment of the prior art) may be raised.

However at the effective filing date of the present application (11/17/03), at least Mohr et al. (WO 97/04804; IDS) already taught the preparation of HSV mutants having a genome from which the γ34.5 genes have been deleted, wherein the HSV mutants are avirulent and are capable of selectively replicating in and destroying neoplastic cells but not normal cells (see at least the abstract and Summary of the Invention). Mohr et al

teach specifically both copies of the γ34.5 genes are deleted using techniques known in the art (page 11, lines 17-24). In an exemplification Mohr et al disclose the preparation and use of a targeting constructing comprising HSV-1 sequences which normally bracket the 34.5 gene into the corresponding positions so as to surround the β-glucuronidase gene **whose expression is under the control of endogenous 34.5 promoter upon recombination with a wild-type HSV virus; and its expression is used for selecting HSV mutants selectively replicating in neoplastic cells** (see at least Figure 1; page 14, line 21 continues to line 5 of page 15; page 20, lines 13-16). The exemplified targeting construct of Mohr et al does not teach explicitly a cassette which is located between the flanking 34.5 gene sequences, comprising: (a) one or a plurality of insertion site; (b) a regulatory nucleotide sequence; and (c) a marker, wherein the nucleic acid sequence encoding the one or a plurality of insertion sites is upstream of the regulatory nucleotide sequence and the nucleic acid sequence encoding the regulatory nucleotide sequence is arranged upstream of the marker. At the effective filing date of the present application, Binns et al. (EP 0353851; IDS) already disclosed numerous versions of homologous recombination plasmids for the insertion of foreign genes into the DNA genome of a fowlpox virus (see at least the abstract; page 13, line 55 continues to line 50 of page 14 and Figures 1, 4-7). In both exemplified Figures 4 and 6, a restriction site (A or C'D') is placed upstream of a promoter which is operatively linked to a foreign gene/marker gene. Binns et al further disclosed that since it is time consuming to determine precisely where the mRNA transcription start is effected by any particular promoter, it is convenient simply to insert

a promoter immediately preceding a foreign gene (page 14, lines 2-6 and Figure 4). Accordingly, it would have been obvious for an ordinary skilled artisan to modify the teachings of Mohr et al by also utilizing at least a targeting construct comprising a cassette comprising a nucleic acid encoding one insertion site upstream of a promoter that is operatively linked to a marker gene for the preparation of HSV mutants having a genome from which the γ34.5 genes have been deleted in light of the teachings of Binns et al. An ordinary skilled artisan would have been motivated to carry out the above modification because at least Binns et al taught that it is convenient to place a promoter immediately preceding a foreign gene in a targeting construct since it is time consuming to determine precisely where the mRNA transcription start is effected by any particular promoter, let alone under the control of an endogenous 34.5 promoter resulting from the incorporation of a targeting gene construct via homologous recombination at the RL gene locus. Moreover, at the effective filing date of the present application Gabant et al (US 2003/0017600) also taught the preparation of **a targeting vector comprising at least an insertion site(s) flanking promoters that are upstream and downstream of a cassette sequence containing one or more selectable genes for expression in eukaryotic cells** (e.g., Neo gene, LacZ, GFP, specific recombinases) (see at least paragraphs 26, 35 and Figure 2). Furthermore, at least Chiocca et al. (US 6,602,499) already taught at least a method of selectively killing neoplastic cells **by a combination of viral mediated oncolysis (including HSV viral mutants) and anti-cancer gene therapy, which approach provides a potentiated oncolytic effect much greater than that provided by either viral mediated oncolysis or gene therapy alone** (see

at least the abstract and col. 9, lines 26-31). Dirks et al (US 6,0602,73) already taught **the preparation and use of multicistronic expression units containing the IRES element, and particularly the advantages over other alternatives including the use of multiple genes in separate expression vectors** (see at least col. 1, line 21 continues to line 21 of col. 2).

Therefore, the technical feature linking the inventions of Groups I-VII does not constitute a special technical feature a defined by PCT Rule 13.2, as it does not differentiate the claimed subject matter a whole over the prior art. Since according to Rule 13.2 PCT the presence of such a common or corresponding special technical feature is an absolute prerequisite for unity to be established, and given that there does not appear to be any other technical feature common to the claimed subject matter as a whole which might be able to fulfill this role, the currently claimed subject matter lacks unity of invention according to Rule 13.1 PCT.

Consequently, the claimed subject matter is restricted into the above Groups of Inventions for the following reasons.

The recombination nucleic acid vector of Group I and the herpes simplex virus of Group III are different compositions having different properties for different uses. For example, the recombination nucleic acid vector of Group I is designed to be incorporated into the genome of a selected HSV via homologous recombination. Additionally, it should also be noted that the HSV of Group III can be prepared without the use of the recombination nucleic acid vector of Group I (e.g., ligation of a cassette via a properly digested mutant HSV genome containing a unique restriction site). The

methods in Groups II and IV-VII are drawn to different methods having different starting materials, different method steps and different end-results. For example, the method of Group IV is directed to a method for generating a recombination nucleic acid vector; the method of Group VIII is directed to viral-mediated oncolysis treatment method; the methods of Groups II and VI are directed to different methods of generating a mutant HSV using the vector of claim 109 and the vector of claim 1, respectively; and the method of Group V does not even require the use of either the vector of claim 109 or claim 1 (via random integration or insertion of a nucleic acid cassette).

Although the recombination nucleic acid vector of Group I and the method of Group IV are related as process of making and product made, it should be noted that the recombination nucleic acid vector can be prepared by a different process other than the method of Group IV (e.g., a 3-way ligation reaction for the first nucleotide sequence, the second nucleotide sequence and the cassette).

Similarly, the HSV of Group III and the methods in Groups II, V and VI are related as process of making and product made, however, it is noted that the HSV of Group III can be made by anyone of the methods of Groups II, V and VI or by another different method such as through the ligation of a cassette with a properly digested mutant HSV genome containing a unique restriction site.

Inventions III and VII are related as product and process of use. In the instant case the HSV of Group III can be used in a screening assay rather for a viral-mediated oncolysis treatment method of Group VII.

Because the currently claimed subject matter lacks unity according to Rule 13.1 PCT for the reasons set forth above, restriction for examination purposes as indicated is proper.

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order

to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.**

Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Applicant is advised that the response to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17 (h).

Species restriction:

Upon electing anyone of the above Inventions, the following species restriction is required wherever it is appropriate for the elected invention. This application contains claims directed to more than one species of the generic invention.

These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

The species are as follows:

1. (a) an encoded bacterial polypeptide; (b) an encoded mammalian polypeptide; (c) an antisense nucleic acid; and (d) siRNA.

2. (a) a ribosome binding site; (b) a constitutive promoter; and (c) an inducible promoter.

3. (a) GFP; (b) EGFP; and (c) a defined nucleotide sequence detectable by hybridization under high stringency conditions with a corresponding labeled nucleic acid probe.

4. A single specific herpes simplex virus strain recited in the Markush group of claim 76.

Applicant is required, in reply to this action, to elect a single species to which the claims shall be restricted if no generic claim is finally held to be allowable. The reply must also identify the claims readable on the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered non-responsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons:

1. Each of the listed species of a component present in a nucleic acid vector or a herpes simplex virus is different structurally and has different properties one from the others.
2. Each of the listed species of vector component is different structurally and has different properties one from the others.
3. Each of the listed species of a marker gene is different structurally one from the others.
4. Each of the listed species of herpes virus strains is different structurally and has different properties one from the others.

Each of the aforementioned species is different structurally and has different properties one from the others. Each different structure can be considered to be a "special technical feature"; and therefore the listed species lack the same or corresponding special technical features.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has

been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

/QUANG NGUYEN/
Primary Examiner, Art Unit 1633